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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/876,549 | 06/07/2001 | John SantaLucia JR. | WSU 0192 PUSP | 7537 |

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EXAMINER

LIN, JERRY

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/876,549

Applicant(s)

SANTALUCIA ET AL.

Examiner

Jerry Lin

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/12/2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 12, 2004 has been entered.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 23. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "higher order" in claims 1, 2, 21, 22, 41, and 42 is a relative term which renders the claims indefinite. The term "higher order" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. A higher order complex may be reasonably interpreted as a complex that has a structure of greater than or equal to a secondary structure. Another interpretation of a higher order complex may be a strand of nucleic acid with a large number of hybridized base pairs. Alternatively, a hybridized strand of nucleic acid with a higher order complex may be any structure that is greater than or equal to the complexity of a strand of nucleic acid hybridized to a complementary strand.

In addition, in claims 1, 21, and 41, the claims recite the limitation of statistically weighing at least one higher order complex in the calculation of hybridization thermodynamics. It is unclear from the claims how statistically weighing at least one higher order complex effects the calculation of hybridization.

Claims 3-20, 23-40, and 43-60 are rejected for their dependence from claims 1, 2, 21, 22, 41, and 42.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 9-15, 21, 25, 29-35, 41, 45, and 49-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lange et al. (US 6,403,314 B1) in view of Lane et al. (US 6,027,884)

Regarding claims 1, 12, 21, 32, 41, and 52, Lange et al. teach a method of predicting nucleic acid hybridization that includes providing a database of thermodynamic parameters (column 15, lines 45-58); receiving hybridization information that represents at least one sequence (column 16, lines 1-10); and calculating the net hybridization thermodynamics including the correction data and hybridization conditions such as temperature (column 11, lines 39-55; column 15, 46-58). In addition, by interpreting higher order complex to mean any structure that is greater than or equal to the complexity of a strand of nucleic acid hybridized to a complementary strand, Lange et al. also teach calculating hybridization thermodynamics wherein the thermodynamics of at least one higher order complex are statistically weighted by accumulating the total

stability for all interactions to a fragment and each is given equal statistical weight. (column 11, lines 1-36). Furthermore, Lange et al. teach implementing their method using a C++ pseudo-code, which would require the use of a computer system as well as a computer readable storage medium (column 16, line 61 – column 17, line 8).

Lange et al., however, does not teach a method where correction data is received, where a first set of data which represents hybridization conditions is received, or where hybridization thermodynamics are statistically weighted.

Lane et al. teach a method of determining the thermodynamics of hybridization that includes receiving correction data such as receiving singlet and doublet values to input into a correction factor (column 38, lines 14-61); receiving a set of data that represents hybridization conditions such as non-sequence specific ligand/DNA interactions between ligand and DNA substrate (column 45, lines 21-35; column 48, lines 11-29);

Regarding claims 11, 31, and 51, Lange et al. also teach wherein the correction data also includes folding correction data (column 15, lines 4-12).

Regarding claim 5, 9, 10, 25, 29, 30, 45, 49, and 50, Lange et al. teach wherein the thermodynamic parameters include DNA, RNA, and DNA/RNA thermodynamic parameters (column 15, lines 18-67).

Regarding claims 13-15, 23-25, and 43-45, Lange et al. teach wherein the hybridization information represents at least one probe and the hybridization thermodynamics are calculated for a plurality of probes for the target (column 15, lines 32- 41).

It would have been obvious to combine the reference of Lange et al. and Lane et al. given that both methods are drawn to determining hybridization thermodynamics. One of Lane et al.'s stated goals is to determine the free energy-parameter of a duplex formed by the hybridization of a single stranded nucleotide (column 2, lines 40-43). Thus it would have been obvious to one of ordinary skill in the art to use a method, such as one disclosed by Lange et al., to determine the hybridization potential of two polymers (column 1, lines 15-25). In addition, both methods are implemented using computational techniques which one of ordinary skill in the art may combine with ease. Thus to would have been obvious to one of ordinary skill in the art to combine the methods of Lange et al. and Lane et al. give their common goals and their common implementation techniques.

Claims 1, 6- 8, 16, 17, 21, 26-28, 36, 37, 41, 46-48, 56, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lange et al. (US 6,403,314 B1) in view of Lane et al (US 6,027,884), as applied to claim 1 above, further in view of Barciszewski et al. (RNA Biochemistry and Biotechnology).

Lange et al. and Lane et al. are applied as above.

Lange et al. or Lane et al. do not explicitly teach using dangling end parameters, coaxial stacking parameters, or terminal mismatch parameters.

Regarding claims 6-8, 26-28, and 46-48, Barciszewski et al. teach using dangling end parameters (p. 21, fourth full paragraph being with "stacking free energies"), coaxial

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stacking parameters (p. 22, first full paragraph), and terminal mismatch parameters (p. 15, third full paragraph beginning with "In addition").

Regarding claims 16, 17, 36, 37, 56, and 57, Barciszewski et al. teach a method wherein the length of the target is longer than the length of the primer or probe (p. 21, fourth full paragraph beginning with "stacking free energies") and a method that includes calculating mismatch parameters (p. 15, third full paragraph beginning with "In addition"). In addition, Lange et al. teach evaluating multiple potential probe molecules to select molecules for high hybridization potential (column 15, lines 32-41).

It would have been obvious to one of ordinary skill in the art to combine the references of Lange et al. and Barciszewski et al. Lange et al. teach a computational method for predicting the hybridization stability for two polymers (see abstract). Barciszewski et al. also teaches a computational method that utilizes the thermodynamics nucleic acids to determine secondary structure (see abstract). Both methods are implemented using computational techniques which one of ordinary skill in the art may combine with ease. Lange et al. further states that is method is extremely flexible and can incorporate many different computational methods (column 6, lines 51-60). In addition, one of Lange et al.'s stated goals is to analyze and list all possible single-fragment and multi-fragment cross-hybridizations between a probe molecule and a target molecule and to find the most stable hybridization (column 5, lines 44-56). To achieve Lange's stated goals, one of ordinary skill in the art would incorporate the method disclosed by Barciszewski et al. to include polymers with dangling ends or

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terminal mismatches to expand the types of polymers Lange et al.'s method can analyze to find the all possible hybridizations and find the most stable hybridization.

Status of the Claims

Claims 1-60 are pending.

Claims 1-60 are rejected.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571) 272-2561. The examiner can normally be reached on 10:30-7:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JL

Ardin H. Marschel 4/5/05
ARDIN H. MARSCHEL
PRIMARY EXAMINER